NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

WARNER LAMBERT COMPANY	:	
	:	Civ. Action No. 99-922(DRD)
Plaintiff,	:	
	:	**O P I N I O N**
TEVA PHARMACEUTICALS USA, INC.	:	
	:	
Defendant.	:	
	:	

Melissa L. Klipp, Esq.
DRINKER BIDDLE & REATH LLP
500 Campus Drive
Florham Park, New Jersey 07932

Bruce M. Wexler, Esq.
Sandra S. Shim, Esq.
PAUL, HASTINGS, JANOFSKY & WALKER, LLP
Park Avenue Tower
75 East 55th Street, First Floor
New York, New York 10022
Attorneys for Plaintiff
Warner-Lambert Company

Allyn Z. Lite, Esq.
Michael E. Patunas, Esq.
LITE, DEPALMA, GREENBERG & RIVAS, LLC
Two Gateway Center, 12th Floor
Newark, New Jersey 07102-5003

David M. Hashmall, Esq.
Annemarie Hassett, Esq.
GOODWIN PROCTER LLP
599 Lexington Avenue
New York, New York 10022

Kenneth A. Cohen, Esq.

Henry C. Dinger, P.C., Esq.
Exchange Place
Boston, Massachusetts 02109
Attorneys for Defendant
Teva Pharmaceuticals USA, Inc.

Debevoise, Senior District Judge

After Teva Pharmaceuticals USA, Inc. ("Teva") appealed from a summary judgment of this court that, among other things, ruled that U.S. Patent No. 4,743,450 ("the '450 patent") owned by Warner-Lambert Company ("Warner-Lambert") was not invalid by reason of non-enablement, the Court of Appeals for the Federal Circuit reversed the ruling with respect to claims 1, 4-10, 12, 16 and 17 based on the lack of express findings in the court's summary judgment opinion and remanded the case for further proceedings on the issue of enablement. Warner-Lambert v. Teva Pharms. USA, Inc., 418 F.3d 1326 (Fed. Cir. 2005).

The issue of enablement was tried before the court on May 2 and 3, 2007. The court heard the testimony of Teva's expert, Gilbert S. Banker, Ph.D., and Warner-Lambert's expert, Gordon L. Amidon, Ph.D. It also received deposition testimony of other witnesses and numerous exhibits. On the basis of this evidence the court finds that independent claims 1 and 16 and dependent claims 4-10, 12 and 17 of the '450 patent are enabled as required by 35 U.S.C. § 112.

I. Background

The invention claimed in the '450 patent is directed to pharmaceutical compositions containing an ACE inhibitor that is stabilized against cyclization, hydrolysis and oxidative discoloration, and a process for stabilizing an ACE inhibitor against cyclization. All of the asserted claims, claims 1, 4-10, 12 and 16-17, require the use of a carbonate and a saccharide for stabilization. Independent claims 1 and 16 are as follows:

1. A pharmaceutical composition which contains:

(a) a drug component which comprises a suitable amount of an ACE inhibitor which is susceptible to cyclization, hydrolysis, and discoloration,

(b) a suitable amount of an alkali or alkaline earth metal carbonate to inhibit cyclization and discoloration, and

(c) a suitable amount of a saccharide to inhibit hydrolysis.

16. A process for stabilizing an ACE inhibitor drug against cyclization which comprises the step of contacting the drug with:

(a) a suitable amount of an alkali or alkaline earth-metal carbonate and,

(b) one or more saccharides.

The '450 patent claims are of the widest breadth. The pharmaceutical compositions of the invention can vary greatly and include "tablets, capsules, sachets, sprinklers, pomades, transdermal compositions, buccal preparations, candy compositions, nasal formulations, ocular compositions, and the like." (DTX 1 at 4:36-41). The '450 patent's only example of a dosage form is a tablet. The patent contemplates a broad array of excipients: "The compositions of the invention may contain suitable quantities of disintegrating agents, carriers, diluents, pigments, binders, colorants, lubricants, and other additives conventionally used in the production of pharmaceutical products." (DTX1 at 3:66-4.2).

Claim 1 covers a drug component comprising a suitable amount of an ACE inhibitor susceptible to cyclization, hydrolysis and discoloration. ACE inhibitors useful in the invention are "any of a group of well-known compounds which have antihypertensive properties." (DTX 1 at 2:9-10). Claim 1 also covers use of pharmaceutically acceptable salts of ACE inhibitors. There are no examples of either ACE inhibitors or salts thereof other than quinapril

hydrochloride.

The '450 patent states that one can use alkali metals and alkaline earth metals at 1-90 percent by weight of the formulation. (DTX 1 at 3:30-41). Carbonates include lithium carbonate, sodium carbonate and bicarbonate, potassium carbonate and bicarbonate calcium carbonate and magnesium carbonate. The examples in the patent use only magnesium carbonate.

The '450 patent states that mannitol, lactose and other sugars are preferred, that mixtures are operable, and that the saccharide component will be from about 5-90 percent by weight. (DTX 1 at 3:54-58). The '450 patent exemplifies only the use of lactose as the saccharide in a range of 16-28 percent.

Claims 16 and 17 and dependent claims 4-10 and 12 present comparable breadth characteristics.

It is Teva's contention that the breadth of these claims and the patent's lack of guidance on how to achieve this vast range of claimed stable formulations or how to use the claimed processes to produce them constitutes a failure to meet the enablement requirement of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . .

II. Legal Standards

The Federal Circuit has explained "that the specification must provide sufficient teaching such that one skilled in the art could make and use the full scope of the invention without undue experimentation." Warner-Lambert Co., 418 F. 3d at 1337. "The key word is 'undue', not

'experimentation,'" In re Wands, 858 F. 2d 731, 737 (Fed. Cir. 1988). That is, the specification need only teach those aspects of the invention that one skilled in the art could not figure out without undue experimentation.

The ultimate determination of whether one skilled in the art could make and use the claimed invention without undue experimentation is a legal one. However, it is a conclusion reached by weighing many factual considerations. "Some of these considerations, commonly referred to as 'the Wands factors,' include '(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.'" Warner-Lambert Co., 418 F. 3d at 1337.

In analyzing enablement, each asserted claim must be analyzed independently, 35 U.S.C. § 282 (dependent claims are presumed valid independently of the validity of other claims). Even if broad claims are proven invalid for lack of enablement, narrower dependent claims may still be enabled and valid. In re Vaeck, 947 F. 2d 488, 496, (Fed. Cir. 1991)

A patent is presumed valid, and the burden of proving invalidity by clear and convincing evidence rests with the challenger. 35 U.S.C. § 282; U.S. v. Telectronics, Inc., 857 F. 2d 778, 785 (Fed. Cir. 1988).

III. Teva's Contentions

For the purposes of this case it has been held that one of ordinary skill with respect to the '450 patent has the following characteristics: a pharmaceutical formulator, that is a person having a working knowledge of drug development and formulation, who has either an advanced degree

in pharmaceutics, chemistry or related science with one or more years of industry experience or a bachelor's degree in pharmaceutics, chemistry or a related science and at least five or more years of industry experience or the equivalent.

Teva juxtaposes the breadth of the claims of the '450 patent against the sparcity of the guidance that the specification provides to the person of ordinary skill in the art. Teva asserts that "[t]he patent only discloses a combination of a single ACE inhibitor (quinapril hydrochloride), a single carbonate (magnesium carbonate) and a single saccharide (lactose) in a single dosage form (tablet) produced by a single process, the steps of which are not disclosed. The '450 patent teaches no scientific principles or mechanisms to guide pharmaceutical formulators in making the numerous choices necessary to practice the '450 patent for formulations beyond this specific combination. Morever, because the patent addresses a relatively new class of compounds and processes of degradation that were little understood at the time, the prior art provided little help. In short, the '450 patent leaves the person of skill to his or her own devices in a blind process of trial and error" (Teva's Pretrial Brief at 1, 2).

It is undisputed that at the time when the '450 patent application was filed, persons of ordinary skill in the art did not know how to stabilize ACE inhibitors against cyclization and certainly did not know how to stabilize against cyclization, hydrolysis and discoloration simultaneously. This was the subject of strenuous efforts of Merck as well as Warner-Lambert.

Teva's expert, Dr. Banker, testified that "[i]n the early 1987 time frame, virtually nothing was known about cyclization as a mechanism of decomposition for drugs in general or ACE inhibitors in particular." (May 2 Tr. at 60). He further testified that "[s]tabilization processes are very challenging . . . There's an enormous number of factors that can influence stability even

when you have [a] single, simple, well understood stability problem" and "[t]he only guidance in the patent that I see are those two examples. (Id.) One drug, one saccharide, one carbonate and pretty close ratios [among the ingredients in the two examples]." (Id. at 61). He summed up his observations, stating "[t]he patent doesn't disclose a mechanism of decomposition . . . [and] the patent also doesn't give any hints as to how to go about stabilizing the system . . . I don't know if I've ever seen such a complicated challenge for a pharmaceutical scientist relative to stabilization." (Id. at 62).

Dr. Banker gave a number of reasons for his opinion that a person skilled in the art as of 1987 would not have been able to practice the full range of claims 1, 4 to 10, 12, 16 and 17 of the '450 patent without undue experimentation (Id. at 59-105):

1. At that time virtually nothing was known about cyclization as a mechanism of decomposition for drugs in general and ACE inhibitors in particular.

2. Even if there is only one instability problem (and infinitely more so if there are three), many different things can influence stability, e.g., the ingredients (including non-drug excipient ingredients), dosage form, environmental conditions, temperature and humidity.

3. The '450 patent encompassed an enormous number of combinations and extremely broad specifications: "I don't think I've ever seen a patent that had such broad claims to literally hundreds of ACE inhibitors. To many different stabilizing agents, the carbonates, the many different saccharides, to perhaps a hundred other drugs there are listed as active pharmaceutical excipients or APIs that are listed in the patent, that are taught that could be combined in a patent with a range of combinations, and the issue of excipients, other ingredients." (Id. at 61).

4. The only guidance given in the specification are the two examples, A and B. Out of

the multitude of possibilities, they incorporate "[o]ne drug, one saccharide, one carbonate, and pretty close ratios. Example[s] A and B are not very divergent as to ratio. The only other guidance is an expression of preference for wet granulation. Those are the only two pieces of guidance in that entire patent." (Id.).

5. Finally, Dr. Banker gave as a reason for his opinion of non-enablement the fact that even apart from the failure to disclose a mechanism of decomposition, "the patent also doesn't give any hints as to how to go about stabilizing the system. Or if they were hints, they are pretty vague hints. And when you don't know where you're going in your development work, in your design of a product, it's not routine. It's very complicated. And when you have so many different permutations and computations [combinations] of things to try that's not routine, and the thing that makes this case really non-routine, your Honor, is you've got three decomposition mechanisms going on at the same time. You've got this cyclization phenomenon which back then the people didn't understand, hadn't seen it before, and in that regard I would call it nascent. You've got the issue of hydrolysis, which is caused by water reacting with drug molecules and breaking them down. And you've got the issue of oxidation, which is a third decomposition mechanism which causes color changes in products. And the thing that, in addition to having three different simultaneous kinetics processes going on, you've got one you don't understand. So I don't know if I've ever seen such a complicated challenge for a pharmaceutical scientist relative to stabilization." (Id. at 62).

Dr. Banker derived from the '450 patent the guidance it gives to a pharmaceutical formulator of ordinary skill in the art, which he characterized as "about the least guidance I can think of." (Id. at 86). The guidance he noted was the ACE inhibitor (quinapril), the saccharide

(lactose) and the carbonate (magnesium carbonate) along with the statement that wet granulation is preferred. But it could not be inferred that lactose and magnesium carbonate would stabilize any ACE inhibitor other than quinapril. Dr. Banker found no guidance in the patent as to the ratio of ingredients that would be used to stabilize any ACE inhibitor other then quinapril.

Addressing initially claim 1, Dr. Banker described the process that a formulator would have to go through in order to arrive at a stabilized formulation within the claims of the patent but using drugs or excipients other than those in Examples A and B. (May 2 Tr. at 91-97). He discounted an approach in which the formulator would start with the relative proportions of the ingredients disclosed in Examples A and B of the '450 patent and then just adjust the ratios up and down until stability was achieved. In his opinion the various carbonates and saccharides, not to mention the excipients, have so many different solubilities and other properties that the experimentation process would be unduly time consuming. He contemplated that it would take minimally 30 to 45 days to determine if a particular formulation produced the necessary stability. If it did not, the formulator would simply have to start over again without the benefit of any guidance within the patent. The process would be complicated, according to Dr. Banker, by the other factors that could affect stability, such as the form of the final product and the excipients used. In summation Dr. Banker concluded:

> A. I'm sorry, 1987 timeframe. So I would be - - I would be very much of the opinion this is not routine testing, there's so much uncertainty. There's so many little known in the prior art. There's such unpredictability in the stability process. There's so little guidance in the patent. For all these reasons, it's a non-routine process, and it's a very time-consuming process. And how on earth you're going to - how on earth you're going to enable all the claims in the patent, and the salts, and the dosage forms and everything else. You can throw those out and just enable what we're talking about primarily today, how to enable the hundreds of ACE inhibitors, the score - - well, the eight mixtures and their combinations, the

> scores of saccharides and their mixtures, and the other active ingredients are already up in the thousands, thousands, and how you're going to enable all the those, it might take a life time. (May 2 Tr. at 96-97).

Dr. Banker applied the same analysis to Claims 4, 6-10, 12, 16 and 17, and in his opinion, despite their differences from claim 1, a person of ordinary skill in the art in early 1987 would not be able to practice the full scope of those claims without undue experimentation. Teva drew upon items in the record in this case to support Dr. Banker's opinion, which was based upon his study of the '450 patent and his extensive experience, that such a person would be unable to practice the full scope of the claims of the patent without undue experimentation.

It was acknowledged that as of February 24, 1987, drug degradation by cyclization had been rarely observed (Amidon Mar. 24, 2007 Dep. Tr. at 100-101). Dr. Brenner testified that prior to Merck's work on the stable formulation of enalapril, no members of his group had had any experience with drugs that cyclize. (May 3-6 Trial Tr. at 601). Nor in early 1987 would a person of ordinary skill in the art have known how or why a saccharide would stabilize an ACE inhibitor against hydrolysis or cyclization. (Amidon Mar. 21, 2007 Dep. at 73-76).

The record reflects the difficulties that Warner-Lambert, Merck and Schwarz Pharma formulators had when, based on pre-February 24, 1987 state of the art, they sought to stabilize ACE inhibitor formulations against the three forms of degradation that are the subject of the claims of the '450 patent. During this effort they were using combinations of ACE inhibitors, carbonates and saacharides and arrived at what Teva characterizes as a number of inoperative embodiments.

Teva points to the following: i) When developing their quinapril hydrochloride product, Warner-Lambert scientists found more than 25 percent degradation in a tablet containing

quinapril, sodium bicarbonate and lactose within the claimed ranges (DTX 59 at WL 036,575 preparation 2 (using base formulation WL 109,452-40, shown in DTX 602)); ii) Warner-Lambert scientists also found that based on stability results, formulations of quinapril hydrochloride, lactose and sodium carbonate within the scope of the asserted claims were not suitable (DTX 507 at WL 027466-67, 027472-73); iii) Warner-Lambert scientists found that "a 1:1 ratio of sodium carbonate to quinapril hydrochloride displayed acceptable stability results for 5 mg tablets . . . but when this ratio was applied for 40 mg tablets the stability was significantly reduced." (DTX 507 at WL 027467). iv) A subsequent Warner-Lambert presentation stated, "Calcium Carbonate, Sodium Bicarbonate and Sodium Hydroxide all fail to stabilize Accupril. Doses of <40 are very difficult to stabilize." (DTX 330 at WL031216).

From this Teva contends, "[t]hus, during their quinapril development, even when using carbonate and lactose, which is all the '450 patent teaches, Warner-Lambert still encountered inoperative embodiments. This shows that merely combining an ACE inhibitor with a carbonate and a saccharide, as taught by the patent, will often lead to inoperative embodiments. Warner-Lambert's unsuccessful attempts with these embodiments are not mentioned in the specification of the '450 patent. Indeed, the patent actually states that with regard to carbonates, '[m]agnesium, calcium, and sodium are preferred.' DTX at 3:33-34. Yet, Warner-Lambert could not stabilize quinapril tablets with the majority of even the carbonates that the '450 patent says are 'preferred.' The problem of inoperative embodiments when using even 'preferred' carbonates is compounded by the breadth of the asserted claims of the '450 patent, which cover ACE inhibitors other than quinapril, dosage forms other than tablets, and a range of carbonates and excipients." (Teva Pretrial Brief at 23-24).

Further, Teva notes that the '450 patent indicates that wet granulation is preferred (DTX 1 at 4:27-28). In fact, according to Teva, Warner-Lambert's documentation establishes that wet granulation was not only preferred but necessary, a fact not disclosed in the patent. Warner-Lambert's "Comprehensive Summary for Quinapril" states that for magnesium/lactose stabilized tablets: "Wet granulation was necessary to create the stable environment. Dry blends were not stable." (DTX 72 at WL 029059). A summary of the development of quinapril tablets prepared much later stated, "wet mixing of the components was essential to inhibition of [cyclization]; simple dry blends were not stable." (DTX 511 at WL 02744).

Process claims 16 and 17 encompass the use of wet granulation, dry granulation and direct compression. The '450 patent indicates that wet granulation is preferred. (DTX 1 at 4:27-28). According to Teva, and as described above, Warner-Lambert experience and information publicly available after the filing of the application for the '450 patent, show that wet granulation is not only preferred; it is required, a subject about which the patent provides no guidance to the person of ordinary skill in the art, or to anyone else.

Teva relies upon the Merck experience to support its contention that without specific and unusual processing conditions, even wet granulated formulations of enalapril, sodium bicarbonate and lactose were not stable. At the first trial Dr. Brenner, one of the inventors of Merck's enalapril product, Vasotec, testified that simply knowing to use wet granulation would not enable a pharmaceutical formulator to stabilize enalapril against cyclization. He cited five critical manufacturing variables that affected stabilization: i) the type of mixing equipment; ii) the duration of mixing; iii) the temperature of mixing; iv) the holding time in the mixer before drying; and v) the particle size of the carbonate used. After four years of experimentation and

research, Merck decided not to patent the process it had developed to stabilize enalapril, believing that the process was so specialized that trade secret protection would prove more valuable than patent monopoly. As Dr. Brenner testified:

> [T]he consensus opinion was that knowing the composition [of the enalapril tablets] above would not have allowed the preparation [of] tablets.

(Brenner First Trial Tr. at 158:5-6).

Teva argues that the Merck's development experience shows that even knowing the combination of ACE inhibitor, carbonate and lactose is not enough to enable a person of ordinary skill to practice the claimed '450 patent invention.

Teva cites Schwarz Pharma's difficulties encountered in its attempt to practice the '450 patent when developing its moexipril tablets. Starting with dry processing, it determined that wet granulation was necessary to stabilize moexipril hydrochloride against cyclization and that its moexipril hydrochloride formulations with sodium carbonate, potassium carbonate or magnesium carbonate did not stabilize against discoloration.

In sum, Teva asserts, the '450 patent's broadest claims encompass a wide range of ACE inhibitors, carbonates, saccharides and proportions thereof, and are unlimited with regard to the acid addition salt of the ACE inhibitor, dose, dosage form and manufacturing process, thus covering potentially thousands of formulations with the dependent claims narrowing this scope only to a limited extent. Also, Teva asserts, that as guidance, the '450 provides only two working examples. Both are formulations of quinapril hydrochloride tablets stabilized with magnesium carbonate and lactose. This extraordinary breadth, this lack of guidance in the patent itself, and evidence of inventors' difficulties in achieving stabilization notwithstanding the

availability of the patent establishes, according to Teva, that the specification of the patent fails to teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. Durel Corp. v. Osram Sylvania, Inc., 256 F. 3d 1298, 1309 (Fed. Cir. 2001).

IV. Discussion

Enablement is a question of law, based upon underlying factual determinations. Falkner v. Inglus, 448 F. 3d 1357, 1363 (Fed. Cir. 2006). The patentee enjoys the benefit of presumptions. A patent is presumed valid, and the burden of proving invalidity by clear and convincing evidence rests with the challenger. 35 U.S.C. § 282; U.S. v. Telectronics, Inc., 857 F. 2d 778, 785 (Fed. Cir. 1988). Further, since the claim scope and the disclosure of the patent specification are both directly before the Examiner during prosecution, there is a presumption that the Examiner reviewed the patent specification for compliance with enablement requirements and found any issued claims to be enabled. Callicrate v. Wadsworth Mfg., Inc., 427 F. 3d 1361, 1374 (Fed. Cir. 2005).

As described at some length above, Teva seeks to sustain its burden of proving non-enablement through two routes: (i) the difficulty a person skilled in the art would have in producing the invention in light of the breadth of the claims and the asserted paucity of guidance provided by the patent and ii) examples of failures to arrive at operative embodiments despite use of combinations of ACE inhibitors, carbonates and saacharides.

Teva relies on Pharmaceutical Res., Inc. v. Roxane Labs, Inc., 2006 WL 3231427 (D.N.J., Nov. 8, 2006), aff'd, 2007 WL 3151692 (Fed. Cir.) (the Federal Circuit opinion being referred to as the "Par case"). This court held that the asserted claims of the '318 and '320 patents were

invalid as a matter of law for lack of enablement. The Federal Circuit Court of Appeals affirmed.

The patents at issue in the Par case related to stable flocculated suspensions of megestrol acetate and methods for making such suspensions. The type and concentration of the surfactant in solution were critical in creating a stable flocculated suspension. Claim 19 of the 318 patent recited: "An oral pharmaceutical composition in the form of a stable flocculated suspension in water comprising: (a) megestrol acetate; (b) at least two compounds selected from the group consisting of polyethylene glycol, propylene glycol, glycerol, and sorbitol; and (c) a surfactant. The Federal Circuit applied the factors set forth in In re Wands, 858 F. 2d 731, 737 (Fed. Cir. 1988), noting initially that "Par sought extremely broad claims in a field of art that it acknowledged was highly unpredictable, therefore Par has set a high burden that its patent disclosure must meet to satisfy the requisite quid pro quo of patent enablement." (Slip Op. at 2).

The Court emphasized the unpredictability of the particular pharmaceutical formulation and that a person skilled in the art would not have any reasonable expectation of success in maintaining a stable flocculated suspension of megestrol acetate once a change in the type or amount of surfactant or wetting agent is made.

Further megestrol acetate was sufficiently unique as a compound such that prior art references teaching how to wet other insoluble compounds provided no guidance with regard to wetting megestrol acetate. Actual experimentation was required.

The Court emphasized the breadth of the claims: "The claims allow the choice of any surfactant in any concentration . . . The language of the claims and the specification both suggest that the claims encompass hundreds of possible surfactants . . . Moreover, nothing in the language of the claims limits the concentration of surfactant. The specification gives a preferred

concentration range for only one surfactant . . . To the extent that Par now suggests that an ordinarily skilled artisan would know that surfactant concentrations over 0.030% weight-per-volume would not work, it follows that a large part of the asserted claims' scope is directed toward inoperative embodiments. The number of inoperative combinations is significant when assessing the experimentation that an ordinarily skilled artisan would need to practice the claimed invention." Id. at 3-4.

The Federal Circuit concluded that Par's evidence of enablement failed to establish a genuine issue of material fact in light of the broad scope of the claims and the highly unpredictable nature of the art. Par's specification disclosed only three working examples utilizing only one new surfactant, as to which the Federal Circuit stated, "[g]iven the highly unpredictable nature of the invention and the extremely broad scope of the claims, these three working examples do not provide an enabling disclosure commensurate with the entire scope of the claims." Id. at 4.

The Federal Circuit rejected the two declarations of Par's expert witnesses on the issue of enablement as conclusory and lack of evidentiary support or specifics as to the experimentation that would be needed to practice the entire scope of the claims. Finally, the Federal Circuit found unpersuasive the fact that the inventor was successful in formulating the claimed composition with seven surfactants, stating that the numerous unsuccessful attempts by Par to practice subject matter within the scope of the claims supported a conclusion of lack of enablement. The Federal Circuit's summarized its ultimate finding as follows:

> Interpreting Dr. Femia's testimony in the light most favorable to Par, that Dr. Femia was successful in formulating the claimed composition with seven surfactants, gives rise to "merely colorable" evidence, and fails to create a genuine

> issue of material fact as to enablement of the full scope of the claims. It is highly relevant that the intrinsic evidence stresses the criticality of the choice of surfactant and concentration. Given this fact, the extraordinarily broad scope of the claims, which encompasses hundreds of surfactants, the high degree of unpredictability of the art, and the minimal guidance provided by the three working examples in the specification, the mere fact that Par's inventors were able to create successfully a stable flocculated megestrol acetate suspension with seven surfactants does not create a genuine issue of material fact regarding enablement.

Id.

The Par case shares with the instant case the fact that its claims are extremely broad and that their formulations are unpredictable. Par, however, is distinguishable on a number of grounds.

In the claims of the '318 and '320 patents, the type and concentration of the surfactant in solution were critical. Par conceded that concentrations over 0.030% weight-per-volume would not work. Thus a large part of the asserted claims' scope was directed toward inoperative embodiments. A contrary situation pertains with respect to the '450 patent. The invention incorporates wide variance in the amounts or proportions of stabilizers and active ingredients and still provides the claimed stabilization. Teva chose different proportions of stabilizers for its quinapril formulation compared to Warner-Lambert's. In the working examples of the patent, the ratios of the ACE inhibitor to carbonate and to lactose are very different, and both formulations are stable.

The Federal Circuit rejected testimony of Par's expert witnesses as conclusory and lacking in evidentiary support or specifics as to the experimentation that would be needed to practice the entire scope of the claims. Teva relies on the testimony of Dr. Banker, which has been summarized above. More persuasive is the testimony of Dr. Amidon supporting his

conclusion that the '450 patent teaches those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. Dr. Amidon's testimony will be discussed later in this opinion.

In Par there was evidence of numerous unsuccessful attempts by Par to practice the subject matter within the scope of the claims. In the present case, despite Teva's efforts to characterize as inoperative embodiments such matters as (i) aspects of Schwarz Pharma's experiment involving formulations of magnesium carbonate, lactose and the ACE inhibitor moexipril, (ii) instances of supposed inability to formulate ACE inhibitors using direct compression or dry granulation, (iii) Merck's numerous unsuccessful experiments during its development of its enalapril formulation, and (iv) Teva's reliance on documents created as Warner-Lambert developed its formulation that purportedly demonstrate inoperative embodiments, none of these instances that Teva proffers are evidence of lack of enablement.

The Schwarz Pharma experiment upon which Teva relies (DTX 548) actually resulted in a stable formulation that was abandoned because it was not bioequivalent. The evidence is insufficient to establish that under no circumstances can there be a formulation of ACE inhibitors using direct compression or dry granulation. If there were such evidence, the enablement requirement is met if, as is the case, wet granulation works to stabilize ACE inhibitor compositions. Merck's extensive efforts, without the benefit of the '450 patent, to develop its enalapril composition and then formulate it so that it could be successfully manufactured, cannot, without more, constitute evidence of undue experimentation. Similarly, the documents that Teva has selected from Warner-Lambert's files are unsupported or explained by adequate testimony. It is impossible to draw inferences from such cryptic statements as "calcium carbonate is not

directly substitutable for magnesium carbonate" (DTX 65, WL 29202).

Thus Par does not provide support for a finding in the instant case that the '450 patent is invalid for lack of enablement.

Atlas Powder Co. v. E.L. DuPont deNemours & Co., 750 F. 2d 1569 (Fed. Cir. 1984) provides useful guidance in analyzing Teva's enablement challenge to the '450 patent. The invention of the '978 patent that was the subject of Atlas was an intimately mixed water-in-oil, water resistant emulsion blasting agent that stabilized the blasting agent that Atlas previously had manufactured and sold. Dupont began making and selling a water-in-oil emulsion blasting agent. Atlas sued for infringement. The District Court held the pertinent claims not invalid under 35 U.S.C. §§ 102, 103 and 112, not fraudulently procured, and infringed. DuPont appealed.

DuPont's challenge on § 112 non-enablement grounds mirror Teva's challenge in the instant case, generally that the broad scope of the claims was not supported by the limited disclosures in the patent, thus failing to enable one of ordinary skill in the art to make and use the claimed invention. DuPont argued that the patent disclosure listed numerous salts, fuels and emulsifiers that could form thousands of emulsions but that there was no commensurate teaching as to what combinations would work. Thus the disclosure was no more than innumerable possibilities from which one skilled in the art would have to select and experiment unduly to find an operable emulsion.

DuPont characterized the examples in the patent as "merely prophetic," with no guarantee that they would actually work. DuPont further noted some 300 experiments Atlas performed before filing the application for the '978 patent. Atlas's records indicated that 40 percent failed. DuPont asserted that Atlas was able to produce suitable emulsions with only two emulsifiers and

contended that the disclosure should be construed to read upon only those two.

The District Court found that the fact that from the ingredients listed in the patent thousands of emulsifiers could be formed was not a bar to enablement, stating that "it would have been impossible for Bluhm to list all operable emulsions and exclude the inoperable ones." The Court further found "such list unnecessary, because one skilled in the art would knew how to select a salt and fuel and then apply 'Bancroft's Rule' to determine the proper emulsifier." 750 F. 2d at 1576.

The District Court found that the "prophetic" examples of the specification were based on actual experiments that were slightly modified in the patent to reflect what the inventor believed to be optimum, and hence, they would be helpful in enabling someone to make the invention.

As to the large number of pre-filing failed experiments, the District Court found that they were not really "failures," rather, they had been designated "failures" because they were not optimal under all conditions. Optimality was not required under all conditions, and "one skilled in the art would know how to modify slightly many of those 'failures' to form a better emulsion." Id. at 1577.

The District Court rejected DuPont's contention that Atlas's ability to produce only two emulsifiers was evidence of non-enablement on a number of grounds: i) DuPont did not prove that the other disclosed emulsifiers were inoperable; ii) the Court credited the testimony of Atlas's expert that he had successfully formed a number of detonable emulsions using a variety of emulsifiers specified in the '978 patent; iii) one skilled in the art would know which emulsifiers would work in a given system; and iv) DuPont's own researchers had little difficulty in making satisfactory emulsions with the emulsifying agents, salts and fuels listed in the '978

patent.

The Federal Circuit agreed with the District Court's analysis. If stated "[t]hat some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive," Id. at 1576. The fact that the list of salts, fuels and emulsions listed in the '978 could form thousands of emulsions did not render the amount of experimentation unduly extensive. The Federal Circuit "agree[d] with the district court's conclusion on enablement. Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude . . . possible inoperative substances . . .'" Id.).

The Federal Circuit concluded that "DuPont has failed to show that the district court erred in determining enablement." Id. at 1577. The circumstances in Atlas closely parallel those in the instant case. The primary concern is whether, in light of the breadth of the claims of the '450 patent, a person skilled in the art would have to perform undue experimentation to produce the invention.

There has been set forth above, at considerable length, the reasons why Teva's expert, Dr. Banker, is of the opinion that the experimentation would be undue. His opinion and the reasons he gives for it are countered by the testimony of Gordon L. Amidon, Ph.D., who, since 1994, has been Professor of Pharmacy at the College of Pharmacy, University of Michigan. His extensive public and private experience in the field of drug formulation includes, since 1986, serving as President or Chairman and Chief Scientific Officer of TSRL, Inc., a private company that specializes in drug development and formulation. He wrote the book on stability of pharmaceutical formulations.

Dr. Amidon testified that one of ordinary skill in the art could readily practice the full scope of the claimed invention through routine experimentation. Examples A and B set forth formulation ingredients and amounts, and specified that the formulation was to be made by wet granulation. He testified that wet granulation was the most common and widely used method for preparing solid dosage forms at the time of the '450 patent, and that the patent expressly taught this method as being preferred. Dr. Amidon further testified that the Examples showed that they were working examples and that the varying ratios of ingredients seen in Examples A and B demonstrated flexibility in designing a stable formulation. Examples A and B are identical to Warner-Lambert's commercial formulations, and Dr. Amidon testified that starting with Examples A and B a formulator of ordinary skill in the art could make other formulations of quinapril hydrochloride. Dr. Amidon cited the backup 40 mg formulation prepared by Warner-Lambert, which achieved stability although it used a different ratio of magnesium carbonate to quinapril and lactose to quinapril and used different amounts and types of excipients.

Dr. Amidon addressed Dr. Banker's contention that the ability of the person skilled in the art to practice the invention was adversely affected by the fact that before the '450 patent the prior art did not disclose the stabilization of an ACE inhibitor with an alkali or alkaline earth metal carbonate and saccharide. This was relevant to the non-obviousness of the invention, but Dr. Amidon explained that it was not necessary to understand the detailed mechanism of degradation in order to prepare stable formulations of an ACE inhibitor using the materials taught in the patent.

Citing the vast number of possible combinations using the ingredients specified in the '450 patent, Dr. Banker's opinion of undue experimentation contemplated that one of skill in the

art would make a formulation, wait 30-45 days to first test it, and then start over if that formulation was not optimal. Dr. Amidon rejected this procedure as contrary to standard practice in pharmaceutical stability testing. Using his 1986 textbook as an illustration, he described how one of ordinary skill in the art would go about making a formulation containing a different ACE inhibitor within the scope of the patent using routine experimentation. One skilled in the art would set up a "fractional factorial" design, allowing the effect of multiple formulation variables (such as five different ingredients and amounts) to be analyzed simultaneously with a limited set of routine experiments run simultaneously.

Contrary to Dr. Banker's opinion that it would not be "rational" to use Examples A and B as reference points for designing new formulations, such a formulator would start from Examples A and B, applying (a) the guidance set forth in the patent specification regarding alternative ingredients, (b) the formulator's own knowledge, experience and available references regarding typical formulation excipients, and (c) information developed in pre-formulation studies for that particular ACE inhibitor, including excipient compatibility studies.

Using the data and trends in the data observed from the stability results of the first set of experiments, the formulator would design a next set of experiments in order to find an optimal formulation. There would be no need to wait a month for each set of tests. Monitoring after several days would permit rejection of the experiment if significant degradation were to occur.

Teva sought to establish lack of enablement not only through Dr. Banker's testimony but also through certain items in the record that Teva claims demonstrates an absence of enablement.

Teva referred to the evidence in the record of Merck's extensive efforts to develop a stable formulation of enalapril. Dr. Brenner and his team had no experience with cyclization

prior to working with enalapril. Merck decided that the difficulty in stabilizing a formulation containing an ACE inhibitor was so great that its product and process would receive greater protection from duplication by preserving them as trade secrets rather than patenting them. Rather than negating enablement, this observation supports enablement. If a patent would make a duplication more likely, it follows that the patent disclosures would facilitate formulation of a stabilized product. In any event, this consideration bears upon obviousness, not enablement, and Dr. Amidon testified persuasively that prior knowledge of the mechanism of cyclization (or hydrolysis) is not a requisite for a formulator to conduct experimentation based upon disclosures in the '450 patent.

As described above, to support its non-operative contention, Teva refers to difficulties Warner-Lambert had when it sought to stabilize quinapril. As the Federal Circuit stated, "[e]ven if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude . . . possible inoperative substances . . .'" Atlas, 750 F. 2d at 1576. There has been no evidence in this case that the number of inoperative combinations is so significant as to force one of ordinary skill in the art to experiment unduly in order to practice the claimed invention.

Teva refers to Schwarz Pharma's difficulties in its efforts to stabilize moexipril, in particular the fact that it started with dry processing before concluding that wet granulation was necessary to stabilize moexipril hydrochloride against cyclization and that its moexipril hydrochloride formulations with sodium carbonate, potassium carbonate or magnesium carbonate did not stabilize against discoloration. Dr. Amidon testified that wet granulation was the most common and widely used method for preparing solid dosage forms at the time of the

'450 patent, and, of course, the patent expressly referred to this method as being preferred. Through continued experimentation Schwarz Pharma derived a stabilized moexipril formulation. The article concerning moexipril that Teva introduced into the record shows that moexipril was stabilized, using the wet granulation technique, by sodium bicarbonate, sodium carbonate and calcium carbonate combined with lactose.

Neither Dr. Banker's testimony nor the episodes occurring during the course of Warner-Lambert's, Merck's or Schwarz Pharma's developmental work establish inoperative embodiments that would cause the need for undue experimentation by a person of ordinary skill in the art. In fact the evidence demonstrates the existence of operative embodiments.

Examples A and B of the patent were operative embodiments of stabilized quinapril. The 20 mg and 40 mg commercial formulations of Warner-Lambert and the 40 mg and 80 mg "backup" formulations of quinapril hydrochloride were additional operative quinapril hydrochloride embodiments made through routine experimentation.

Teva prepared additional operative embodiments of quinapril hydrochloride; compare its 5 mg formulation shown in PTX 258 with the 5 mg formulation of Example A of the '450 patent. Teva concedes that in the development of its 40 mg formulation it started from the Warner-Lambert formulation and then pursued only routine experimentation. It required less than one month from the time the first formulations were created to design the final commercial 40 mg formulation of its product.

At the May, 2007 trial Dr. Amidon testified that calcium carbonate appeared to demonstrate a stabilizing effect when used with quinapril, and on deposition Warner-Lambert's inventor testified that calcium carbonate showed stability.

Teva's proofs fail to establish by clear and convincing evidence that the '450 patent does not meet § 112's requirement that it contain a description that enables one skilled in the art to make and use the invention without unduly extensive experimentation. The '450 patent provides working examples and other guidance for practicing the invention. A patent can support extremely broad claims even if some of the embodiments are inoperative. Atlas Powder, 750 F. 2d at 1576-77. The existence of inoperative embodiments does not establish lack of enablement so long as one of ordinary skill in the art can identify the inoperative embodiments without unduly extensive experimentation. Atlas Powder, Id. Dr. Amidon's testimony is persuasive evidence that one of ordinary skill in the art could identify inoperative embodiments without unduly extensive experimentation.

In the case In re Wands, the Federal Circuit found enablement and reversed the PTO's decision despite the applicant's admission that inoperative embodiments resulted the first four times the applicant tried to practice the invention: "[e]ven if we were to accept the [Patent Office's] 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff." 858 F. 2d 731, 739-40 (Fed. Cir. 1988). Dr. Banker and Teva have not approached establishing a success-failure rate that would cast doubt upon the '450 patent's enablement.

The foregoing discussion addresses claim 1 of the patent. However, the same or similar considerations apply to independent claim 16[1] of the patent and to dependent claims 4-10, 12 and

[1] Claim 16 does not require that the ACE inhibitor be stabilized against hydrolysis or discoloration. Nevertheless, Dr. Banker's testimony on non-enablement of Claim 16 was supported in part by the assertion that Claim 16 required stabilization against three forms of

17. In his testimony Dr. Amidon provided additional reasons why claims 4, 10 and 16 are enabled.

The enablement of narrower independent claims must be separately analyzed. In re Vaeck, 947 F. 2d 488, 496 (Fed. Cir. 1991). Claim 4 of the '450 patent is narrowly drawn and fully meets Teva's enablement challenge. If rewritten in independent form it would read:

> 4. A pharmaceutical composition which contains:
>
> (a) a drug component which comprises a suitable amount of an ACE inhibitor which is susceptible to cyclization, hydrolysis, and discoloration,
>
> (b) a suitable amount of magnesium carbonate to inhibit cyclization and discoloration, and
>
> (c) a suitable amount of a saccharide to inhibit hydrolysis

Teva has not advanced plausible grounds to argue that this narrowly drawn claim is not enabled.

V. Conclusion

For the reasons set forth above a judgment will be entered to the effect that claims 1, 4-10, 12, 16 and 17 of the '450 patent are enabled.

/s/ Dickinson R. Debevoise
DICKINSON R. DEBEVOISE
U.S.S.D.J.

November 29, 2007

---

degradation. Teva offered no evidence that one of ordinary skill in the art court not prepare formulations stabilizing an ACE inhibitor against just cyclization without undue experimentation.